PATENT COOPERATION TREATY

IPM/JLL

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

Levy, David J.
GLAXOSMITHKLINE
Five Moore Drive
PO Box 13398
Research Triangle Park, NC 27709
ETATS-UNIS D'AMERIQUE

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Rule 71.1)

Date of mailing *(day/month/year)*	03.09.2004
Applicant's or agent's file reference PU4758WO	**IMPORTANT NOTIFICATION**

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US 03/22717	21.07.2003	23.07.2002

Applicant
SMITHKLINE BEECHAM CORPORATION et al

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. **REMINDER**

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

The applicant's attention is drawn to Article 33(5), which provides that the criteria of novelty, inventive step and industrial applicability described in Article 33(2) to (4) merely serve the purposes of international preliminary examination and that "any Contracting State may apply additional or different criteria for the purposes of deciding whether, in that State, the claimed inventions is patentable or not" (see also Article 27(5)). Such additional criteria may relate, for example, to exemptions from patentability, requirements for enabling disclosure, clarity and support for the claims.

Name and mailing address of the international preliminary examining authority:

European Patent Office - P.B. 5818 Patentlaan 2
NL-2280 HV Rijswijk - Pays Bas
Tel. +31 70 340 - 2040 Tx: 31 651 epo nl
Fax: +31 70 340 - 3016

Authorized Officer

Cardenas, C

Tel. +31 70 340-3370

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference PU4758WO	**FOR FURTHER ACTION**	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/US 03/22717	International filing date *(day/month/year)* 21.07.2003	Priority date *(day/month/year)* 23.07.2002
International Patent Classification (IPC) or both national classification and IPC A61K31/519		
Applicant SMITHKLINE BEECHAM CORPORATION et al		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 8 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the opinion
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand 04.02.2004	Date of completion of this report 03.09.2004
Name and mailing address of the international preliminary examining authority: European Patent Office - P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk - Pays Bas Tel. +31 70 340 - 2040 Tx: 31 651 epo nl Fax: +31 70 340 - 3016	Authorized Officer Langer, O Telephone No. +31 70 340-1972

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/US 03/22717

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

Description, Pages

1-71 as originally filed

Claims, Numbers

1-20 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).

   ☐ the language of publication of the international application (under Rule 48.3(b)).

   ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   ☐ contained in the international application in written form.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority in written form.

   ☐ furnished subsequently to this Authority in computer readable form.

   ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   ☐ the description, pages:

   ☐ the claims, Nos.:

   ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/US 03/22717

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

   ☐ the entire international application,

   ☒ claims Nos. 1-20

   because:

   ☒ the said international application, or the said claims Nos. 1-13 and 20 with respect to industrial applicability relate to the following subject matter which does not require an international preliminary examination (specify):

   see separate sheet

   ☒ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. 1-20 are so unclear that no meaningful opinion could be formed *(specify)*:

   see separate sheet

   ☒ the claims, or said claims Nos. 1-20 are so inadequately supported by the description that no meaningful opinion could be formed.

   ☐ no international search report has been established for the said claims Nos.

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

   ☐ the written form has not been furnished or does not comply with the Standard.

   ☐ the computer readable form has not been furnished or does not comply with the Standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-20
	No:	Claims	
Inventive step (IS)	Yes:	Claims	1-20
	No:	Claims	
Industrial applicability (IA)	Yes:	Claims	14-19
	No:	Claims	

2. Citations and explanations

   see separate sheet

Re Item III.

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

III.1. Clarity of the claims (Article 6 PCT); disclosure of the invention (Article 5 PCT)

III.1.1. Second medical use claims 14-18 and method claims 1-11 and 20 are not acceptable under Article 6 PCT. The therapeutic application is functionally defined by a mechanism of action, namely misregulation of a protein kinase, of a serine/threosine kinase, of GSK3, of a tyrosine kinase or of TIE2, which does not allow any practical application in the form of a defined, real treatment of a pathological condition (disease).

III.1.2. The expression "pharmaceutically acceptable derivatives" in present claims 1, 14 and dependent claims 2-13, 20 and 14-19 relates to compounds defined by reference to a desirable characteristic or property, namely their capability to release "upon administration to a mammal [...] (directly or indirectly) a compound of the present invention or an active metabolite thereof" (page 11, line 30 to page 12, line 2).

The claims cover all compounds having this characteristic or property, whereas the application provides support within the meaning of Article 6 PCT and disclosure within the meaning of Article 5 PCT for only a very limited number of such compounds.

Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). An attempt is made to define the compounds by reference to a result to be achieved. In the present case such a wording is not allowable because it appears possible to define the subject-matter in more concrete terms, namely by using chemical formulae.

In particular, the expression "metabolite" is not clear as it is not possible to determine into which chemical compounds the compounds of formula (I) of the present invention are being metabolised by or in the body of a mammalian patient.

III.1.3. For the above reasons, an International Search Report (ISR) has been established for only those parts of the claims that appear to be clear, supported and disclosed, namely those parts relating to the use of compounds according to formula (I) in the treatment of a pathological condition (disease) selected from the group consisting of type 2 diabetes, hyperlipidemia, obesity, CNS disorders, neurotraumatic injuries, baldness or hair loss, atherosclerotic cardiovascular disease, hypertension, polycystic ovary syndrome, ischemia, immunodeficiency and cancer, or to provide immune potentiation, cf claims 12, 13 and 19.

III.1.4. The ISR for the present application has been limited to subject-matter as defined under item III.1.3. This International Preliminary Examination Report has been established only for those parts of the subject-matter of the present claims for which an International Search has been performed, namely those parts that have been specified under item III.1.3.

III.1.5. Remarks

III.1.5.1. Dependent claims 16-18 have been drafted as method claims but refer to use claim 14. They have been assumed to read "The use of claim 14 (...)", cf. page 8, lines 25-30.

III.1.5.2. The expression "serine/threosine kinase" in claims 8 and 15 has been assumed to read "serine/threonine kinase", cf. page 3, line 18 of the description.

III.1.5.3. The expression "piperadinyl" in claim 4 has been assumed to read "piperidinyl", cf. page 7, line 31 of the description.

III.2. Industrial applicability; Rule 67.1(iv) PCT

Claims 1-13 and 20 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

Re Item V.

Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability

V.1. The following documents are referred to:

D1: WO-A-0038675, cited in the application
D2: US-A-5593997
D3: WO-A-0119829
D4: WO-A-9814449

V.2. Novelty (Article 33(2) PCT)

The subject-matter of claims 1-20 is new in the sense of Article 33(2) PCT.

No use of compounds according to formula (I) in medical treatment has been disclosed in the prior art.

Consequently, any claim relating to a first or subsequent medical use of compounds according to formula (I) is new in the sense of Article 33(2) PCT.

V.3. Inventive step (Article 33(3) PCT)

The subject-matter of claims 1-20 does involve an inventive step in the sense of Article 33(3) PCT.

V.3.1. Problem to be solved

The problem to be solved by the present application is the provision of methods and medicaments for the treatment of a disease or condition characterised by a misregulation of a protein kinase, in particular for the treatment of type 2 diabetes, hyperlipidemia, obesity, CNS disorders, neurotraumatic injuries, baldness or hair loss, atherosclerotic cardiovascular disease, hypertension, polycystic ovary syndrome, ischemia, immunodeficiency and cancer, and to provide immune potentiation.

V.3.2. Solution

The solution proposed by the applicant is to use a compound according to formula (I).

V.3.3. Prior art

Document D1

discloses that conditions associated with a need for the inhibition of the protein kinase GSK-3, including diabetes, hair loss and cancer, can be treated by bisindole maleimides, indole aryl maleimides and indolocarbazoles, which are particularly potent and selective inhibitors of GSK-3 (page 5, paragraph 4).

Document D2

discloses that certain 4-aminopyrazolo[3,4-d]pyrimidines are inhibitors of tyrosine kinases and can therefore be used in the treatment of tyrosine kinase dependent diseases and conditions, including psoriasis, cancer, immunoregulation (graft rejection), atherosclerosis, rheumatoid arthritis and angiogenesis (e.g. tumor growth, diabetic retinopathy) (column 4, lines 19-25).

Document D3

discloses that certain 4-aminopyrazolo[3,4-d]pyrimidines are inhibitors of the endothelial cell specific receptor tyrosine kinase Tie-2, and could therefore be useful in the treatment of rheumatoid arthritis and in situations of inappropriate neovascularisation (page 8, paragraph 3).

Document D4

discloses that 4-amino-1H-pyrazolo[3,4-d]pyrimidines inhibit "the tyrosine kinase activity of the receptor for epidermal growth factor and can be used, for example, for epidermal hyperproliferation (psoriasis) and as antitumor agents" (abstract).

V.3.4. Comparison of application and prior art

The 1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl-hydrazones of the present application and the bisindole maleimides, indole aryl maleimides and indolocarbazoles of document D1 belong to entirely different chemical classes.

The 1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl-hydrazones of the present application and the 4-amino-1H-pyrazolo[3,4-d]pyrimidines of documents D2-D4 show significant structural differences.

V.3.5. Inventive step analysis

A person skilled in the art, with the knowledge of any of documents D1 to D4, alone or combined, would, without the exercise of any skill or ability beyond that to be expected from him, not expect - based on this knowledge - a similar activity for the structurally unrelated or at least significantly different compounds of the present invention.

V.3.6. Consequently, the subject-matter of claims 1-20, as far as relating to subject-matter as defined under items III.1.3 and III.1.4, encompasses an inventive step in the sense of Article 33(3) PCT.

V.4. Industrial applicability (Article 33(4) PCT)

V.4.a. Product claims 14-19

The subject-matter of claims 14-19, directed to the use of a compound of formula (I) in the manufacture of a medicament is considered susceptible of industrial application in the sense of Article 33(4) PCT.

V.4.b. Method claims 1-13 and 20

For the assessment of the present claims 1-13 and 20 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.